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Ictal bradyarrhythmias and asystole requiring pacemaker implantation: Combined EEG–ECG analysis of 5 cases

Roisin Bartlam [a], Rajiv Mohanraj [a,b,*]

[a] University of Manchester, Manchester, UK
[b] Department of Neurology, Salford Royal NHS Foundation Trust, Salford M6 8HD, UK

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ABSTRACT

Background: Seizures can lead to cardiac arrhythmias by a number of mechanisms including activation/inhibition of cortical autonomic centers, increase in vagal tone through activation of brainstem reflex centers, and respiratory failure. Ictal asystole (IA) is a potential mechanism underlying sudden unexpected death in epilepsy (SUDEP). We analyzed the clinical features of 5 patients who developed IA requiring pacemaker implantation.
Methods: Patients with ictal arrhythmias were identified from the video-telemetry and ambulatory EEG database at Greater Manchester Neurosciences Centre, as well as an independent epilepsy residential care facility. Only those who had IA requiring pacemaker implantation were included in the analysis. A total of 5 patients were identified.
Results: Of the 5 patients with IA, 4 were female. All 5 patients had focal epilepsy, and four had temporal lobe epilepsy. Ictal asystole occurred with focal seizures with impairment of awareness. Seizure onset was left-sided in 2 patients, right-sided in one, left-sided onset with switch of lateralization in one, and nonlateralized in one patient. Three patients had hippocampal sclerosis, one of whom had undergone epilepsy surgery, one had traumatic encephalomalacia of the temporal lobe, and one patient had no lesions detected on MRI. Interictal epileptiform activity was more pronounced during sleep in all patients. Asystole occurred in association with sleep-related seizures in 4 of 5 patients.
Conclusions: Ictal asystole (IA) occurred in association with sleep-related seizures in 4 out of 5 cases, predominantly in patients with temporal lobe epilepsy. These findings may be of relevance to SUDEP.

1. Background

Alterations in cardiac rhythm are common during seizures, and tachycardia is seen in up to 64% of temporal lobe seizures [1]. Ictal bradyarrhythmias (IB), including ictal asystole (IA), are rare but potentially serious occurrences. Ictal asystole has been proposed as a possible mechanism behind sudden unexplained death in epilepsy (SUDEP) [2]. The pathophysiology of IA/IB remains unconfirmed, and three possible mechanisms have been postulated: 1) activation or inhibition of cortical autonomic centers, including the insula [3–5]; 2) increase in vagal tone through activation of autonomic reflex centers located in the brainstem [6]; and 3) secondary to respiratory failure precipitated by the seizure [6,7]. Antiepileptic drugs (AEDs) have also been suggested as potentially contributing to seizure-related cardiac dysfunction; the introduction of carbamazepine has been shown to slow atrioventricular conduction, relatively increase sympathetic tone, and suppress autonomic function [8,9].

Temporal lobe epilepsy (TLE) has been shown to be a consistent risk factor for IA/IB [1,7,10]. Previous studies have suggested possible correlations between seizure lateralization and IA. It is thought that the left temporal lobe influences parasympathetic cardiac control, while the right affects the sympathetic [11,12]. Although one study suggested that left hemisphere seizures were a risk factor for IA [10], others have reported cases of IA associated with right-sided seizures [7]. It is likely that there is no consistent relationship between IA and seizure lateralization.

Ictal asystole/ictal bradyarrhythmias (IA/IB) should be considered in those who present with unexplained atonia and physical falls during focal seizures and those whose seizure activity is associated with marked pallor [7,13]. Definitive diagnosis relies upon capturing an episode of IA/IB, either through combined EEG/ECG recording or through the use of an implantable loop recorder [3]. While the implications of IA/IB are not fully understood, it is linked with an increased likelihood of traumatic falls. Additionally, IA could be a potential mechanism of sudden unexplained death in epilepsy (SUDEP) [2], although one recent study has suggested that postictal asystole has greater implications for SUDEP than asystole during a seizure [14]. While there is no confirmed link between seizure-related asystole and SUDEP, there is a need for

* Corresponding author at: Department of Neurology, Salford Royal NHS Foundation Trust, Stott Lane, Salford M6 8HD, UK. Tel.: +44 161 206 4626; fax: +44 161 206 2993.
E-mail address: Rajiv.Mohanraj@srft.nhs.uk (R. Mohanraj).

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greater understanding of IA, including its risk factors and the potential implications. We report five cases of IA/IB treated with implantation of permanent pacemaker, to identify possible risk factors for the IA/IB.

2. Methods

All patients (n = 5) with IA/IB confirmed by ambulatory EEG and video-telemetry monitoring were identified from the epilepsy monitoring unit at Greater Manchester Neurosciences Centre (GMNC) as well as an independent residential assessment center. Cases were identified from urgent cardiology consults sent from the epilepsy monitoring units. Clinical and demographic data were collected by review of patient records.

The following variables were examined: age at epilepsy onset, type of epilepsy, seizure type, MRI abnormalities, antiepileptic medication used, interictal EEG changes, ictal EEG and ECG changes, seizure lateralization, sleep-related epileptiform activity, and symptoms. The clinical features that should increase suspicion of IA were identified from the common features of the 5 cases. We did not seek ethics committee approval for this retrospective review, as all data were collected as part of routine clinical care. All patients had consented at the time of video-telemetry for the recordings to be used for teaching research and publication.

3. Results

3.1. Demographics

Of the five patients with EEG–ECG-recorded IB, four were female. The mean age was 42.6 years (range from 21 to 62 years; Table 1). None of the patients were known to have cardiac disease.

3.2. Epilepsy history

All 5 patients had refractory focal epilepsy. Duration of epilepsy ranged from 6 years to 57 years. Four of the patients had a diagnosis of temporal lobe epilepsy, while patient 3 was thought to have focal extratemporal epilepsy. For all five patients, the main seizure type was focal seizures with altered consciousness. Patient 1 had epilepsy caused by traumatic brain injury, with brain MRI scan demonstrating encephalomalacia in the left medial subfrontal lobe and left inferior temporal gyrus of the midtemporal lobe. Patient 2 had evidence of right mesial temporal sclerosis (MTS), and patients 4 and 5 had left MTS. Patient 5 had previously undergone left anterior temporal lobectomy. Brian MRI was normal in patient 3. Antiepileptic drugs (AEDs) taken by the patients are summarized in Table 1. All patients except patient 1 were taking carbamazepine as part of their AED regimen.

3.3. Interictal EEG

Interictally, bilateral temporal epileptiform activity was seen in patients 1, 2, and 3. Patient 1 demonstrated spikes and sharp waves with phase reversal in the anterior temporal regions, more frequently on the left. Patient 2 displayed intermittent slow wave activity of 6–8 Hz with sharpened appearance in the right anterior temporal region. Patient 3 had right hemispheric spike and slow wave activity, associated with runs of raised amplitude slow waves. Patient 4 demonstrated occasional slow wave activity of 3–7 Hz over the left frontotemporal region. Patient 5 had bursts of raised amplitude sharp wave activity at 6–7 Hz lasting for approximately 1–4 s in the left anterior temporal region. All patients exhibited an increase in interictal epileptiform discharges during sleep.

3.4. Ictal recordings

Patient 1 had bradyarrhythmia identified during a clinical seizure on cardiac monitoring using implantable loop recorder and had a permanent pacemaker inserted, prior to ictal recording using ambulatory EEG. The patient had experienced nocturnal episodes of becoming confused, as well as falls prior to implantation of pacemaker. During ambulatory EEG, he reported a 'spinning sensation' but no loss of awareness or recall. The EEG showed rhythmic theta/delta discharge in the right anterior temporal region. This was associated with fall of heart rate from 78 to 40 bpm for 35 s, but pacemaker was not activated on this occasion.

Patient 2 had seizures arising from sleep. She opened her eyes, sat up, picked up her glasses, and after 20 s, slumped back and was unresponsive. The fall occurred prior to IA. The EEG showed rhythmic theta activity in the right anterior temporal region, followed by rhythmic theta/delta discharge over the left hemisphere. Ictal asystole developed approximately 11 s after seizure activity started in the left hemisphere and lasted 42 s. The EEG was of low amplitude for 30 s (Fig. 1).

Patient 3 also had seizures during stage 2 sleep. She sat up and exhibited flapping movements of the right hand. Her head turned to the left, and she rubbed the right side of the face with the left hand. This was followed by large amplitude proximal movements of the limbs. The patient then fell backwards, which occurred around the time of IA onset but may have preceded it. The EEG was obscured by movement artifact, and seizure lateralization was not possible. Episodes of asystole occurred towards the end of all five recorded seizures; the length of which ranged from 14 to 42 s.

Patient 4 woke from sleep and demonstrated chewing and sucking movements of the mouth, distortion of face and automatisms of the right hand, and scissoring movements of the legs. The EEG showed sharp waves and irregular delta activity, evolving in frequency up to 5 Hz in the left midposterior temporal region (T3 and T5), followed by

Fig. 1. An EEG/ECG recording demonstrating temporal lobe seizure associated with ictal asystole. Ictal EEG onset was seen over right anterior midtemporal region, in the form of rhythmic theta–delta activity. After 45 s, ictal rhythm stops on the right and, 3 s later, reappears over the left midtemporal region. A few nonpropagated p waves appear at the onset of left-sided EEG activity, and complete asystole develops after a further 12 s. Asystole lasted for 42 s.

Table 1
Clinical and epidemiological details of 5 patients with ictal bradyarrhythmias.

Patient	Age M/F	MRI brain	AEDs at time of IA/IB	IA during sleep-related seizure	History of atonia or unexpected fall
1	60 M	Left temporal encephalomalacia	Sodium valproate, lamotrigine	No	Atonia
2	62 F	Right mesial temporal sclerosis	Levetiracetam, carbamazepine	Yes	Atonia
3	51 F	Normal	Carbamazepine	Yes	Fall
4	38 F	Left mesial temporal sclerosis	Carbamazepine, lamotrigine, topiramate	Yes	No
5	21 F	Left mesial temporal sclerosis	Carbamazepine	Yes	Fall

flattening of EEG at the time of IA. Slow wave activity on EEG resumed as cardiac activity recovered. There was initial bradycardia for 8 s, followed by IA at the end of the seizure, which lasted 21 s.

Patient 5 also had seizures arising from sleep. She opened her eyes, sat up, and shouted. She then started walking out of the room when IA occurred. There was tachycardia at seizure onset, followed by bradycardia leading to 29 s of IA. After 10 s of IA, she became atonic and fell. The EEG showed sharp wave activity in the left anterior regions, followed by generalized delta activity.

All patients underwent permanent pacemaker implantation. No patients reported falls after implantation of pacemaker, although focal seizures with impairment of awareness and/or recall continued to occur in all 5 patients. It was not possible to ascertain whether IA/IB without falls continued to occur during seizures, as timing of seizures was not routinely recorded during pacemaker checks. Data regarding pacemaker activation were only available for patient 1, who continued to have IB with seizures, with pacemaker activation in a proportion of episodes (Table 2).

4. Discussion

Ictal asystole (IA) is a rare but potentially serious phenomenon that should be considered in patients with focal seizures, who present with the red flag symptoms of atonia, unexpected falls, and extreme pallor. However, all cases of IA recorded in our patients occurred during nocturnal seizures. Descriptions of typical red flag symptoms may not be forthcoming in patients who have predominantly nocturnal events, and concomitant EEG/ECG monitoring is required to identify IA/IB. Previous studies have identified temporal lobe epilepsy as a risk factor for IA. In our series of 5 patients, 4 had TLE, with one patient having undergone left temporal lobectomy. Although one patient was described as having extratemporal focal epilepsy, semiology and interictal EEG were suggestive of involvement of the temporal lobe in the seizures. Some previous studies have suggested a link between the lateralization of seizure onset and incidence of IB, although the relationship is not consistent [15,16]. Two of our patients had seizure onset in the right hemisphere and two in the left hemisphere; seizure onset was unclear in the fifth patient. Therefore, there was no clear link in this group of patients between lateralization of seizure onset and IA/IB.

The most striking finding in our study is the association of IA/IB with nocturnal seizures, with 4 out of 5 patients experiencing IA in association with seizures arising from sleep. These patients also exhibited an increase in interictal activity during sleep. Our series suggests a potential link between nocturnal epileptiform activity and IA. One previous study has suggested a link between sleep and rates of ictal tachyarrhythmias but did not specify whether IA/IB occurred [16]. As nocturnal seizures are also a known risk factor for SUDEP [9,12], further research into the possible connection between nocturnal epileptiform activity and the risk of IA is required.

All five patients within the case study had a cardiac pacemaker inserted after the first episode of IB. However, the risk of reoccurrence of IB has not been fully ascertained, and it has been suggested that there is little to be gained from pacemaker insertion [17]. Strzelczyk et al. have suggested that a cardiac pacemaker should be inserted for ictal IA/IB, only in patients who continue to have seizures in spite of optimal treatment with AEDs, and after consideration of epilepsy surgery [18].

Gastaut in his sentinel paper on EEG findings during syncope described a sequence of EEG changes starting with hypersynchronous slowing followed by EEG attenuation [19]. However, as opposed to patients suffering from vasovagal syncope, patients with IA have impairment of consciousness because of seizure rather than cerebral anoxia, and hypersynchronous EEG activity seen during IA is more likely to be due to ictal activity rather than cerebral anoxia. The EEG characteristics of IA are likely to be different to that of syncope, because of the differences in pathophysiology.

Our series adds to the reported cases of IA/IB in the literature and highlights the need for further examination of both the predictive factors of IA and the short- and long-term risks of IA/IB. As a small retrospective study, data presented have limitations. Cases were drawn from 2 epilepsy monitoring units where patients were admitted for a variety of reasons including diagnosis of recurrent spells, presurgical

Table 2
Interictal and ictal EEG and ECG changes seen in 5 patients with ictal bradyarrhythmias.

Patient	Interictal EEG	Nocturnal increase in IED	Hemisphere involved	Semiology	Ictal EEG	ECG changes seen
1	Bilateral temporal sharp waves, more frequent on the left	Yes	Right	Vertiginous aura	Rhythmic theta–delta right anterior temporal region for 28 s.	40 bpm for 35 s (from 78)
2	Sharpened slow wave activity right temporal regions	Yes	Right–left	Arousal → manual automatism → fall	Rhythmic 5- to 6-Hz discharge right anterior temporal region for 2 s, followed by rhythmic 5- to 6-Hz activity over left anterior temporal region for 25 s. Then of low amplitude for 30 s.	42 s, asystole
3	Spike and slow wave activity, right hemispheric	Yes	Unclear	Arousal → right hand automatisms → hypermotor	Possible generalized attenuation, EEG then obscured by movement artifact.	Asystole, 14–43 s
4	Intermittent rhythmic theta–delta activity over left anterior temporal region	Yes	Left	Arousal → orofacial, right hand automatism → bipedal automatism → fall	Rhythmic delta evolving into theta discharge left frontotemporal region with spikes over the left midposterior temporal region. EEG attenuates during asystole, postictal left sided slow.	Bradycardic for 8 s, asystole for 21 s
5	Left anterior temporal sharp waves	Yes	Left	Arousal → vocalization → leaving behavior → fall	Slow wave activity in the theta/delta range, then 5 Hz sharp waves left frontal followed by generalized delta. EEG isoelectric during asystole.	29 s, asystole

assessment, and cognitive impairment. Therefore, a precise denominator is not available to calculate incidence figures. In addition, our observation of nocturnal seizures being associated with IA/IB has not been tested in comparison with a control group. To our knowledge, no other case series have noted association of IA/IB with nocturnal seizures. While the association seen in this uncontrolled study may be spurious, the possible link between nocturnal epileptiform activity and the risk of IA/IB should be explored further, particularly given potential links to SUDEP.

Conflict of interest

The authors have no conflict of interest to declare.

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